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The Seasonality of Rhinovirus Infections and Its Implications for Clinical Recognition

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ABSTRACT

Background: Rhinoviruses are the most common cause of acute respiratory infections. Isolation of rhinoviruses occurs in a distinct and consistent seasonal pattern that can be used to help determine whether an acute respiratory illness is caused by a rhinovirus.

Objective: This article reviews information on the seasonality of rhinovirus infection derived from early and recent studies of rhinovirus occurrence and treatment.

Methods: PubMed was searched from 1965 to the present to identify all potentially relevant papers. The search terms used were *rhinovirus* and *seasonality*. A total of 1998 papers were screened.

Results: Rhinoviruses comprise more than three quarters of viruses circulating in early autumn. In some years and perhaps some geographic areas, spring is an even more important time for rhinovirus transmission. Although overall rates of respiratory illness are lower in summer, rhinoviruses are the most frequently isolated virus at this time of year. Other viral agents, including influenza viruses and respiratory syncytial virus (particularly with parainfluenza virus), predominate in the winter. Thus, for most of the year, rhinoviruses are the cause of the majority of acute viral respiratory infections.

Conclusion: Understanding the seasonal incidence of rhinovirus infection may help determine how best to employ currently available antirhinoviral agents in patients presenting with symptoms of an acute viral respiratory infection.

Key words: rhinovirus, acute viral respiratory infection. (*Clin Ther.* 2002;24:1987–1997)

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INTRODUCTION

Respiratory infections constitute the most common acute illness worldwide and the most important cause of loss of productive time due to an acute condition.¹ The etiology and characteristics of these mainly viral illnesses have long been understood.²⁻⁴ Rhinoviruses play a major role in acute respiratory illnesses, as was recognized in early studies employing only standard virus-isolation techniques.⁵⁻⁸ Their full importance as a cause of viral respiratory infection became yet more apparent with the discovery of polymerase chain reaction (PCR) technology and its application to the rhinoviruses.^{9,10}

Given the unavailability of measures to prevent or treat these infections, it is only in the past decade that interest in the rhinoviruses and their importance in viral respiratory infection has grown. Treatments for human rhinovirus infection are now under development. For example, pleconaril, an antiviral drug specific to picornaviruses, is currently being investigated for its activity against rhinoviruses.¹¹⁻¹³ The recent focus on these viruses has highlighted the prevalence of rhinoviral respiratory infection, whose symptoms can last up to 3 weeks and may cause discomfort, restriction of activity, and lost days from work or school,¹⁴ and may precipitate or exacerbate such conditions as otitis media and asthma.¹⁵⁻¹⁷

The identification of rhinovirus infections remains a major clinical concern. Influenza, another common respiratory infection, is detected in part by its well-recognized seasonality.¹⁸ Prediction by the relative frequency of symptoms is effective only during the defined influenza season. When an acute viral respiratory infection is suspected, information

about the seasonal incidence of rhinovirus infections may help physicians determine whether use of an antiviral agent is indicated. Thus, this article reviews data on seasonality based on recent knowledge emerging from studies of the occurrence and treatment of rhinoviruses.^{10,19,20}

MATERIALS AND METHODS

Potentially relevant articles were identified through a search of PubMed from 1965 to the present using the search terms *rhinovirus* and *seasonality*. For inclusion in the review, a study had to have observed the occurrence of rhinovirus infection in a defined population for ≥ 2 years. A total of 1998 papers were screened, most of them of a virologic nature and not useful in determining seasonal variations in rhinovirus frequency.

In addition, a reanalysis was carried out on data on the incidence of illness from the Tecumseh Study of Respiratory Illness.^{21,22} The Tecumseh study was conducted over an 11-year period. The collection of data started in late 1965 and ended in 1981, with a hiatus from 1971 through 1976. Although there have been other longitudinal investigations of rhinovirus infection, the Tecumseh study was unique in several respects. First, it observed the occurrence of respiratory illnesses in a defined 10% sample of a single American community. Second, it identified all illnesses prospectively on a weekly basis, mainly by telephone, so that the reporting can be considered essentially complete and representative. Third, it identified causative agents by collecting nasal and throat swabs from patients reporting a respiratory illness within 2 days of onset. It supplemented these results by

monitoring antibody titers in blood specimens collected on a biannual schedule. Details of the study methods have been reported elsewhere.²¹

The occurrence per 1000 respiratory infections was reported weekly for >4 years. Also reported was the proportion of total isolates represented by particular isolates during specified times over the study period.²¹ These proportions were based on the standard isolation techniques available at the time. As a result, they would have underestimated the proportion of respiratory infections caused by rhinoviruses.

The extent to which ordinary virus isolation will underestimate total rhinovirus identification, using PCR plus isolation as a standard, has ranged from 1.3 to 3.1^{19,23}; that is, isolation frequencies would need to be multiplied by this factor to produce true rates of identification. Based on data col-

lected later in the Tecumseh study, it was estimated that 34% of all illnesses in a year are attributable to rhinoviruses, but that without the benefit of PCR, 23% of these illnesses would have been unknown at that time.^{22,24} If, conservatively, half of these illnesses were attributed to rhinovirus, the overall percentage of illnesses that were of rhinoviral etiology was 45.5%. This value was then used to adjust the observed seasonal proportions for the >5 years of observation, summarized by month, to a single mean frequency (Figure 1).

RESULTS

Early Studies of Seasonality

In the temperate zone, respiratory infections are traditionally associated with the colder part of the year. Data from a se-

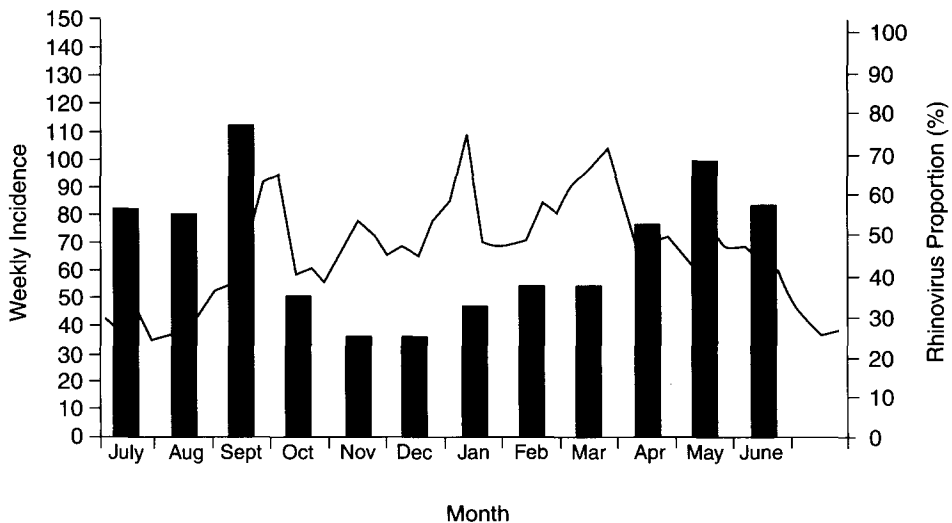


Figure 1. Weekly incidence of total respiratory illnesses per 1000 (graph) and monthly proportion of these illnesses estimated to be rhinoviral (bar chart). Tecumseh, Michigan, summary estimates. Adapted from Makela et al¹⁹ and Monto et al.²⁴

ries of longitudinal studies conducted during the first half of the 20th century showed that these illnesses, including influenza and “grippe,” occurred 5 times more frequently than the next most frequent type of acute illness.^{25,26} When the temporal occurrence of all respiratory illnesses was examined, their incidence was found to increase sharply in September. In fact, this was the most consistent feature in the seasonal pattern of what the Cleveland Family Study^{4,27} later termed “common respiratory illnesses.” That study, conducted from 1948 to 1957, followed ~86 households (2692 person-years) associated with the Case Western Reserve University health care systems. Respiratory viruses such as influenza could be identified at the time the Cleveland study was conducted, but many—including rhinoviruses and respiratory syncytial virus (RSV)—could not. Health care professionals identified the onset of acute illnesses and characterized symptoms during weekly visits. They observed a sharp increase in the frequency of illness beginning in September and continuing through March. The illnesses were commonly associated with fever and sore throat only in the winter months. Non-febrile syndromes are now recognized as characteristic of rhinoviral illnesses.

Frequency of Rhinovirus in the Tecumseh Study

The weekly occurrence of all respiratory infections in a general population was reported from data collected over the first 4 years (1965–1969) of the Tecumseh study.²⁸ These rhinovirus prevalence data were adjusted for the fact that neither organ culture, which had been used in studies of rhinovirus etiology in the United

Kingdom,²⁹ nor the PCR technique was available at the time the Tecumseh study was conducted. Data were summarized by week for the incidence of illness and by month for the proportion of illness that was rhinoviral (Figure 1).

The beginning of July is sometimes termed the start of the respiratory year in the Northern Hemisphere. Starting from this point, the frequency of respiratory illness was low during the summer, although rhinoviruses were the predominant infectious agent. The weekly incidence of respiratory illnesses increased sharply at the beginning of September, when rhinoviruses represented ~77% of disease-causing viruses. The total incidence of respiratory illnesses dropped in October, as did the proportion of rhinoviral infections. Parainfluenza viruses predominated during the late autumn through early winter, along with the occurrence—often on an alternate-year cycle—of laryngotracheobronchitis, or “croup.” In mid-winter, the total incidence of respiratory illnesses again rose, with influenza viruses predominating in most years, particularly influenza A (H3N2). Later in the winter, outbreaks of influenza (predominantly influenza B) in some years resulted in a high overall incidence of total respiratory illnesses; influenza A (H1N1) also occurred during this period.²⁴ Winter was the period in which rhinoviruses, although present, constituted a less important proportion of all respiratory viruses. In spring, however, while the frequency of all respiratory illnesses declined somewhat, the proportion caused by rhinoviruses increased. The dominance of rhinoviruses continued through the summer, despite the overall incidence of respiratory illnesses being relatively low. These data indicate the perennial nature

of rhinoviruses and their importance in late autumn, spring, and summer.

A similar trend in the incidence of rhinovirus was observed during the later years of the Tecumseh study.¹⁴ From 1976 to 1981, rhinoviruses were again identified in all months. Unlike Figure 1, Figure 2 shows the results as the distribution of rhinoviruses isolated in all months of the year. Nonetheless, peaks in the incidence of rhinoviruses were still apparent in the autumn and spring; in fact, they may have been more predominant in the spring than they were between 1965 and 1971. Although fewer rhinoviruses were isolated in the summer than in other seasons, the infrequency of other viruses during this period meant that rhinoviruses were still the most common virus isolated in the summer months.²¹

Other Population-Based Studies

Just as the Tecumseh study was starting, investigations into the occurrence of rhinovirus infections were under way in a population of insurance company personnel in Charlottesville, Virginia.³⁰ Although confining the study to this population may have limited generalizability of the results to the overall population, it was possible to identify the seasonality as well as the incidence of rhinoviral illness. Because the incidence was based on virus isolation, the only method available at the time, the results should be viewed as an underestimate. Figure 3 shows the rate of rhinovirus illness (1000/person-days) and the percentage of persons from whom rhinovirus was isolated.³⁰ The peaks in both the rate of rhinoviral illness and

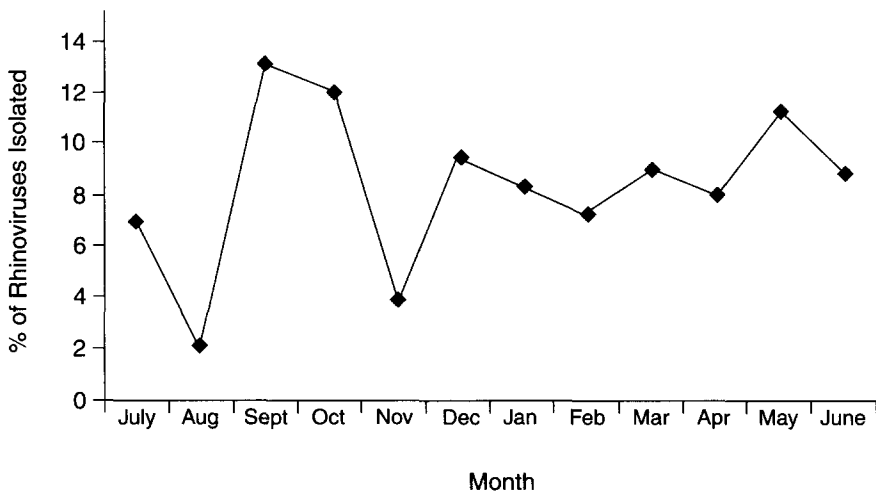


Figure 2. Percentage of rhinoviruses isolated each month in Tecumseh, Michigan, 1976–1981. Adapted from Monto et al.¹⁴

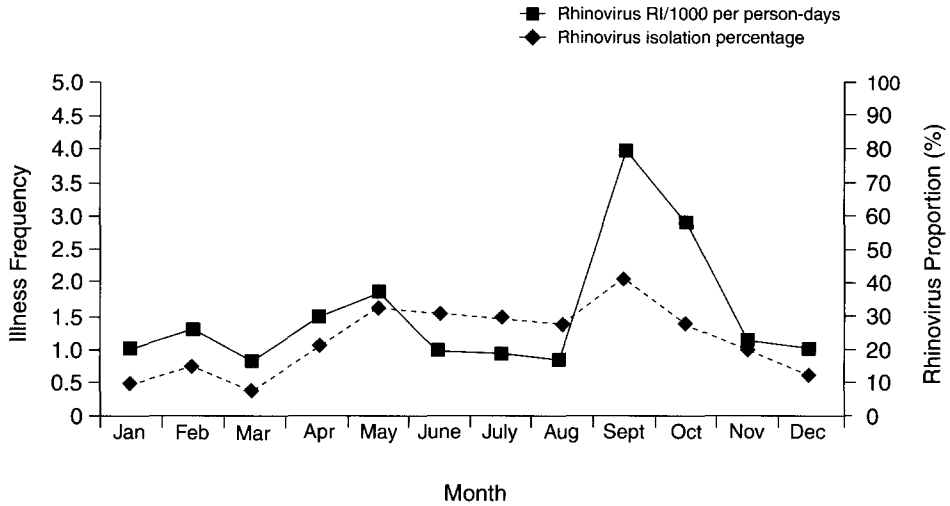


Figure 3. Variation in the frequency of rhinovirus isolation in sampled illnesses and rates of rhinoviral respiratory illness (RI) over 3 years. Adapted from Gwaltney et al.³⁰

rhinovirus yield in autumn were large, with a much less prominent peak in spring. In the early years of the Tecumseh study,^{8,18,21} the spring peak in rhinovirus incidence also was not as prominent as in later years, perhaps reflecting a change over time.

At approximately the same time, 2 Virus Watch studies were under way, one in New York City⁷ and the other in Seattle, Washington.³¹ Rhinoviruses were identified by isolation in the New York study, even though isolation techniques were only under development at the time. After the first month of that study, the greatest number of isolates were identified in April and May, and then in August through October. The methodology was more advanced in the Seattle study, and far more viruses were isolated. Over the period from 1965 to 1969, numbers of isolates were highest in May and next highest in September and October. These

observations are of interest, as Seattle has a far different climate from that in the East (New York) or the Midwest (Tecumseh, Michigan).

More Recent Confirmation of Seasonality

In general, overall seasonality patterns of respiratory infections have been constant over time. Parainfluenza viruses occur mainly in late autumn through early spring, although they can be identified in almost all months. Influenza viruses and RSV are found in winter and sometimes in the spring. Although no longitudinal, population-based studies have been conducted recently, data from current investigations in special populations confirm that the overall seasonal pattern of rhinovirus incidence has remained constant over time.

Studies of antiviral agents with antirhinoviral activity, particularly interferon alfa,

were conducted in the 1980s, mainly in university student populations.^{32,33} These studies used traditional cell-culture isolation techniques for the recovery of rhinoviruses. Studies conducted in winter identified influenza as the primary circulating virus, with rhinoviruses infrequently identified. Those conducted in the autumn months demonstrated high isolation rates of rhinovirus.³²⁻³⁴ The isolation rate of rhinovirus was highest in September and began to drop in October, accompanied by an increase in the frequency of isolation of parainfluenza virus (Figure 4).³⁴

In the 1990s, reverse transcriptase (RT)-PCR methods were gradually incorporated into studies for the identification of rhinoviruses.^{19,23} The RT-PCR method finally adopted overcame the initial problem of the large number of serotypes. In studies carried out in Finland over 1 year,²⁰ a major occurrence of rhinoviruses

was observed in September and October, although these viruses were most frequently isolated in April. In 1994, picornavirus was detected in 82% of students with defined colds at the University of Virginia, Charlottesville.²⁰ In recent clinical trials of the antipicornavirus agent pleconaril conducted in September and October,^{12,13} the prevalence of picornaviral infections was ~65%. This is consistent with the 77% proportion of rhinoviruses in September estimated based on the Tecumseh study.

DISCUSSION AND CONCLUSIONS

Interest in the frequency and characteristics of what is now termed the “common cold” began early in the 20th century, in large part because of the recognition that these were the most common infections in individuals of all ages.^{2,3} This interest led

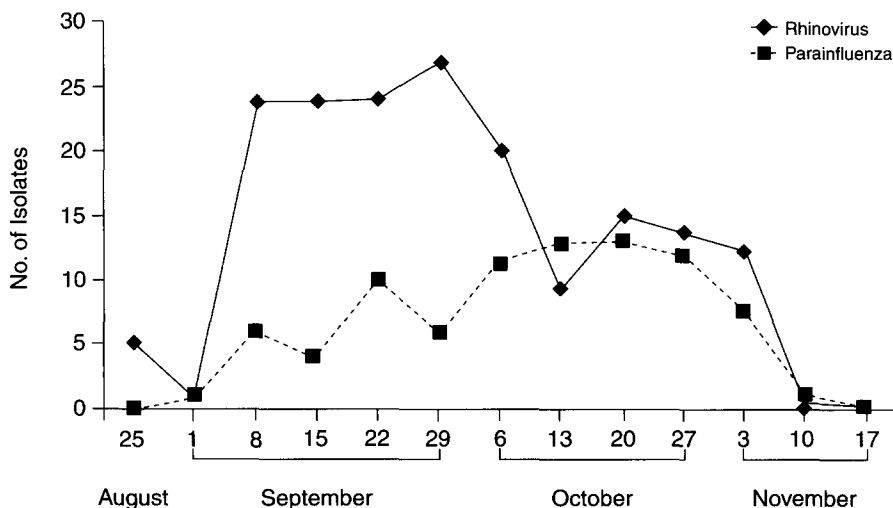


Figure 4. Total number of rhinoviruses and parainfluenza viruses isolated per week in Tecumseh, Michigan, during autumn 1985. Reprinted with permission from Monto et al.³⁴

to identification of the major causative agents, principally the rhinoviruses, at a time when identification was often followed by development of a preventive vaccine.⁸ However, unlike rubella and measles, for which vaccines quickly became available, rhinoviruses were found to be present in large numbers of serotypes, and protection was type specific.¹⁴ Thus, vaccines were not feasible, and other methods of control, such as the use of antiviral agents, became the primary focus. One such compound, pleconaril, is now in development for both the treatment and prevention of common colds.^{12,13} Given that this syndrome can have nonpicornaviral causes, the question arises under what circumstances this drug should be used.

The seasonal pattern of rhinovirus isolation can help determine whether rhinovirus is likely to be the cause of an acute respiratory illness. Rhinoviruses represent by far the largest proportion of respiratory viruses circulating in autumn. In some years, and perhaps in various geographic areas, spring is an even more important time for rhinoviral transmission.^{7,31,35} Although overall illness rates are lower in summer, rhinoviruses and often enteroviruses make the picornaviruses the single major viral pathogen at this time of year. It is only in winter that other infective agents predominate—influenza viruses and RSV, particularly along with parainfluenza virus. Thus, for most of the year, rhinoviruses are the most prominent single cause of acute viral respiratory infections, although other viruses are circulating. Reanalysis of data from the Tecumseh study has allowed quantification of the proportion of illnesses each year that are rhinoviral. As indicated above, more recent studies have confirmed the im-

portance of rhinoviruses in the autumn,^{12,13,20,32-34} indicating a consistent seasonal pattern.

Another method of distinguishing between potential viral causes of respiratory infections is the use of clinical predictors. This method is often applied informally in clinical trials through the inclusion and exclusion criteria. Using this approach, clinical trials conducted in the autumn, including September, have reported an increased proportion of respiratory illnesses caused by rhinoviruses (~65%).^{12,13} Predictors have also been successfully developed for influenza, resulting in correct identification of influenza in up to 87% of selected episodes of respiratory illness during a defined influenza season.^{36,37} In combination with an understanding of the seasonal pattern of occurrence, application of similar methods to picornaviruses may facilitate the appropriate use of antirhinoviral drugs.

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